

# Coronaviruses and SARS-CoV-2: A Brief Overview

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In late December 2019, several cases of pneumonia of unknown origin were reported from China, which in early January 2020 were announced to be caused by a novel coronavirus. The virus was later denominated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and defined as the causal agent of Coronavirus Disease 2019 (COVID-19). Despite massive attempts to contain the disease in China, the virus has spread globally, and COVID-19 was declared a pandemic by the World Health Organization (WHO) in March 2020. Here we provide a short background on coronaviruses, and describe in more detail the novel SARS-CoV-2 and attempts to identify effective therapies against COVID-19. (Anesth Analg XXX;XXX:00–00)

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## IMPLICATIONS OF CORONAVIRUS INFECTIONS FOR ANESTHESIOLOGISTS AND INTENSIVISTS

Because they provide care for COVID-19 patients and frequently perform procedures that generate aerosol (eg, endotracheal intubation, open suctioning, nebulized treatments), anesthesiologists and intensivists are especially at risk to be exposed to the novel coronavirus, putting them at a very high risk for infection. This is demonstrated by a recent publication showing that health care workers have a higher infection rate compared to the normal population.<sup>1</sup> In addition,

given that anesthesiologists and intensivists care for these patients, they should have basic knowledge of SARS-CoV-2 and the course of COVID-19 to effectively treat these patients and to optimally protect themselves.

## WHAT ARE CORONAVIRUSES AND WHERE DO THEY COME FROM?

CoV are found globally in humans and many different animal species. They are classified in the Orthocoronaviridae subfamily (order: Nidovirales, subordination: Cornidovirineae, family: Coronaviridae).<sup>2</sup> CoV can be grouped into 4 genera, including  $\alpha$ -/ $\beta$ -/ $\gamma$ -/ $\delta$ -CoV and  $\alpha$ - and  $\beta$ -CoV can infect mammals, while  $\gamma$ - and  $\delta$ -CoV primarily infect birds.

CoV are enveloped viruses with a lipid membrane derived from the host cell, in which viral surface proteins are embedded. The proteins protruding from the viral membrane (especially the spike [S] protein) give these pathogens their characteristic halo-like appearance under the electron microscope, which has led to the name corona (Latin: garland, crown).<sup>3</sup>

All CoV have in common that their genome is in the form of a single-stranded ribonucleic acid (RNA) with positive polarity, meaning that the base sequence of the RNA is in the 5'→3' orientation and corresponds to the later messenger RNA (mRNA). With a length of 26.4–31.7 kilobases, the genome of CoV is the largest RNA genome of all known RNA viruses.<sup>4</sup>

Besides a number of nonstructural proteins including the RNA-dependent RNA polymerase (RdRp), the viral RNA encodes 4 essential structural proteins, namely the nucleocapsid (N) protein surrounding the RNA genome and 3 membrane proteins: the S-glycoprotein, the matrix (M) protein, and the envelope (E) protein.<sup>5</sup> The S-glycoprotein on the surface of CoV can attach to the cellular receptor, angiotensin-converting enzyme 2 (ACE2) on the surface of human cells.<sup>6</sup> ACE2 is found in the lower respiratory tract

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of humans and regulates both the cross-species and human-to-human transmission.<sup>7</sup>

CoV have a high mutation rate due to their error-prone RdRp, which is responsible for the duplication of genetic information.<sup>8</sup> In addition, homologous recombinations often occur in CoV.<sup>9</sup> These properties have contributed to a great diversity of CoV in nature, which enables these viruses to infect numerous species.

The first coronavirus described was isolated from chicken embryos in 1937, the Infectious Bronchitis Virus (IBV).<sup>10</sup> Since then, numerous CoV have been detected in a wide variety of animals, including wild animals, farm animals, and pets. They are divided into the genera of the mammalian-associated  $\alpha$ - and  $\beta$ -CoV and the bird-associated  $\gamma$ - and  $\delta$ -CoV.

Various CoV are important in veterinary medicine such as transmissible gastroenteritis coronavirus (TGEV) or porcine epidemic diarrhea virus (PEDV) that can cause severe diarrhea in pigs. The spectrum of coronavirus diseases in animals ranges from mild to severe intestinal, respiratory, or systemic diseases.<sup>11</sup> However, there are also many coronavirus infections in animals that do not appear to cause any symptoms. The presence of CoV in a wide variety of animal species strongly suggested that these pathogens are of zoonotic origin and are transmitted from wild animals to humans.

In particular, the SARS pandemic, in 2002–2003, has led to an increasing number of studies in wild animals on all continents. The greatest diversity of CoV has so far been detected in bats.<sup>12</sup> This has led to the hypothesis that at least the more recent CoV introductions to humans were originally bat viruses that spread to an intermediate animal (eg, the Himalayan palm civet for SARS-CoV and the dromedary camel for the Middle East respiratory syndrome [MERS]-CoV), which then exposed humans to the viruses. However, it can be assumed that there are still some gaps in the detection of zoonotic CoV in wild animal populations. In particular, the data situation for economically and/or politically unstable regions of the world is still incomplete.<sup>12</sup>

### CORONAVIRUSES IN HUMANS

The first human coronaviruses (HCoV) were described in the 1960s and were designated HCoV-229E and HCoV-OC43.<sup>13,14</sup> There are now 4 endemic HCoV known (HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1) that circulate worldwide in the human population. In most cases, these endemic HCoV cause relatively mild diseases of the upper and lower respiratory tract and are estimated to account for about a third of all “common colds” in humans. Asymptomatic infections have also been described. In some cases, especially in immunosuppressed

individuals, children, or persons with existing pulmonary diseases, progression to acute respiratory failure can also occur.<sup>15</sup>

The situation completely changed with the appearance of the SARS-CoV.<sup>16</sup> This virus caused serious human respiratory diseases in China in 2002–2003. Approximately 8000 people were affected by the disease at that time, with case fatality rate (mortality rate) of around 9.5%. SARS-CoV spread could be stopped by the rapid development of a detection method and extensive measures to isolate infected individuals. Subsequent studies in wild animals showed that SARS-related CoV are found in bats and civet cats, hence it was assumed that the virus spread from the civet cat to humans, followed by human-to-human spread.<sup>17</sup>

While no human infections with the original SARS virus have been reported since 2004, another CoV dangerous for humans emerged in 2012. The MERS-CoV was isolated for the first time from a patient who was hospitalized with acute pneumonia in Saudi Arabia.<sup>18</sup> By 2019, around 2500 MERS-CoV infections have been reported in humans, with about a 30% case fatality rate.<sup>14</sup> The main risk area for MERS-CoV infections is the Arabian Peninsula. Infections were reported to be both through human-to-human transmission and through contact with dromedaries (camels). These animals appear to represent a reservoir for MERS-CoV.<sup>19</sup>

### SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

At the end of December 2019, China reported the increasing occurrence of pneumonia in the city of Wuhan, Hubei province. In January 2020, a novel  $\beta$ -CoV was identified as the cause.<sup>20</sup> When the virus was first isolated from pneumonia cases in Wuhan, China, in December 2019, it was named 2019 novel coronavirus (2019-nCoV). As more information and genetic analyses became available, the virus was given the official name of SARS-CoV-2 by the International Committee for Taxonomy of Viruses, while the WHO named the disease caused by the virus, COVID-19.

The genome of the new coronavirus shows similarities to other  $\beta$ -CoV found in bats.<sup>20</sup> SARS-CoV-2 is 96.2% identical to a bat CoV RaTG13, whereas it shares 79.5% identity to SARS-CoV. It can therefore be assumed that the virus originally came from bats and has been transmitted over time to other animal hosts and ultimately to humans.

Although the degree of diversification of SARS-CoV-2 is lower than that of, for example, influenza viruses, the divergence of 2 prevalent evolution types of SARS-CoV-2, L type ( $\approx$  70%) and S type ( $\approx$  30%), was reported.<sup>21</sup> According to this study, strains in L type, derived from S type, are evolutionarily more

aggressive and contagious. It is clear now that SARS-CoV-2 also uses ACE2 as a cellular receptor to infect humans.<sup>22</sup>

SARS-CoV-2 is efficiently transmitted from person-to-person and has thus able to spread rapidly across all continents in our globalized world. In the resulting COVID-19 pandemic, 601,478 people have been infected and 27,961 patients have died so far (as of March 28, 2020, source: Johns Hopkins University).

### THE CLINICAL PICTURE

As an emerging acute respiratory infectious disease, COVID-19 primarily spreads through the respiratory tract, by droplets, respiratory secretions, and direct contact.<sup>23</sup> In addition, it has been reported that SARS-CoV-2 was isolated from fecal swabs and blood,<sup>24</sup> indicating the possibility of multiple routes of transmission. However, this needs further clarification.

The current data suggest an incubation period of 1–14 days, in most cases 3–7 days. The virus is highly transmissible in humans and causes severe problems especially in the elderly and people with underlying chronic diseases. COVID-19 patients typically present with specific, similar symptoms, such as fever, malaise, and cough.<sup>25,26</sup> Most adults or children infected with SARS-CoV-2 have presented with mild flu-like symptoms, but a few patients are in critical condition and rapidly develop acute respiratory distress syndrome (ARDS), respiratory failure, multiple organ failure, and even death.<sup>27</sup>

According to a recent report, the common clinical manifestations of COVID-19 included fever (88.7%), cough (67.8%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%), and headache (13.6%).<sup>28</sup> A minor number of patients manifested gastrointestinal symptoms, with diarrhea (3.8%) and vomiting (5.0%). Fever and cough were the dominant symptoms, whereas upper respiratory symptoms and gastrointestinal symptoms were rare. The case fatality rate increases with the severity of illness and can reach up to 49% in critically ill patients.<sup>1</sup> Unfortunately, no specific therapeutic options are currently available. Only supportive measures can be applied at the moment.<sup>29</sup>

### SEARCHING FOR ANTI-COVID-19 DRUGS

There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. There are several worldwide efforts at developing vaccines against SARS-CoV-2. However, it is already clear that these vaccination strategies will not be available until 2021 at the earliest and will thus not be of any help for immediate countermeasures. Thus, antiviral drugs are urgently needed.

New drug licensing as well as repurposing the indications for drugs that are already in clinical use

for other diseases would be the most promising options in the short term. Several of these drug candidates have been proposed and tested, including the human immunodeficiency virus (HIV) drug lopinavir/ritonavir, the antimalarial drugs chloroquine and hydroxychloroquine, and remdesivir, an inhibitor of RNA polymerase with in vitro activity against multiple RNA viruses, including Ebola. However, the results of many of these initial trials suffer from small sample sizes and/or nonrigorous study design.

When lopinavir/ritonavir was tested in a rigorous randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection, no benefit was observed beyond standard care.<sup>30</sup> While a recent trial using hydroxychloroquine was more promising and showed that treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients,<sup>31</sup> this study included only a small number of individuals and therefore considered to have very limited validity. Preclinical studies suggested that remdesivir (GS5734) could be effective for both prophylaxis and therapy of HCoV infections.<sup>32</sup> This drug was positively tested in a rhesus macaque model of MERS-CoV infection<sup>33</sup> and has been reported to treat the first case in the United States of COVID-19 successfully.<sup>34</sup> Accordingly, 2 large clinical trials, NCT04252664 for mild/moderate COVID-19 and NCT04257656 for severe COVID-19, were initiated in China, with an estimated end date in early April 2020.

Similarly, the current lack of valid, rigorous clinical studies has prompted many clinical trials around the world. As one example, Europe has begun large joint clinical studies of experimental drugs to treat COVID-19. The trials will include 3200 patients in the Netherlands, Belgium, Luxembourg, the United Kingdom, France, and Spain, to test the clinical efficacy of the antiviral drugs remdesivir, lopinavir/ritonavir (+/– interferon), and hydroxychloroquine (NCT04315948). ■

### DISCLOSURES

**Name:** Stephan Ludwig, PhD.

**Contribution:** This author helped write and revise the manuscript.

**Name:** Alexander Zarbock, MD.

**Contribution:** This author helped write and revise the manuscript.

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